Bias and fraud in medical research: a review[1]

A V Pollock FRCS **Mary Evans** BA
Scarborough Hospital, Scarborough, North Yorkshire YO12 6QL

'If a man will begin with certainties, he shall end in doubts; but if he will be content to begin with doubts, he shall end in certainties' (Bacon 1605). Four centuries later, one of the greatest of contemporary philosophers – Sir Karl Popper – has consistently maintained that knowledge advances by refutation of false doctrines and not by verification of true ones (which, indeed, can never be completely verified). 'Error is unavoidable; it can be rational, and when responsibly made and honestly reported, is not even culpable' (Laor 1985).

The desire to verify an hypothesis rather than to seek to refute it can be responsible for the suppression of deviant data. There is a fine distinction between bias, which may afflict honest investigators, and fraud, which is always dishonest. Even a true statement can be tainted by bias, and Ronald Fisher concluded that Mendel's published figures on the genetics of peas were so close to the expected ratio of 3:1 that it would have taken 'an absolute miracle of chance' to produce them (Hamblin 1981).

Avoidance of bias

In biomedical research the results of an experimental regimen are usually compared with those of a control regimen. In one of the first controlled clinical trials, James Lind (1753) 'on board the Salisbury at sea' took 12 sailors suffering from scurvy and treated them in six different ways. 'Their cases were as similar as I could have them'. The two who were given oranges and lemons were cured, the rest were not (Fisher's exact test, $P=0.015$).

Such use of contemporary non-random controls can, however, easily lead to bias, and it was to avoid this that the principle of random selection of experimental and control groups was expounded by Ronald Fisher (1925) soon after he was appointed to Rothamsted Agricultural Experimental Station. He realized that the quality of the soil in neighbouring fields could differ profoundly and that trials of different fertilizer treatments would be biased if they were applied to seed which was consistently sown in plots the fertility of which was different from that of the controls.

Randomization was not, however, widely practised in clinical trials until Austin Bradford Hill (Medical Research Council 1948) introduced central randomization in the MRC trial of streptomycin in pulmonary tuberculosis. The whole purpose of randomization is to minimize bias; the clinician must have no control over the allocation of patients to one or other arm of the trial and preferably neither he nor the patient should know which treatment has been given. Bias will enter if the allocation can be foreseen, because it allows clinicians to exclude eligible patients from the allocated treatment group if they have a particularly good (or particularly bad) prognosis. Ideally all eligible patients should be randomized but, particularly in multicentre trials, forgetfulness or contrariness will result in a proportion of such patients being omitted. Furthermore, the requirement of informed consent usually means that a certain number of patients will refuse to enter the trial. These numbers must be recorded, because if there are more than 10% the results of the trial cannot be applied to all patients with the disease being studied.

Exclusions happen before randomization. Withdrawals take place after randomization, and the opportunities for bias are even greater. In any publication of a controlled clinical trial, both the number of withdrawals and their fate must be mentioned. If a trial is analysed by the clinician responsible for setting it up, he may be tempted to withdraw any patient who has

[1]Accepted 18 July 1985

0141–0768/85/011937–04 $02.00/0

shown an anomalous outcome. For this reason, analyses should be done by a research coordinator, without the help of the investigator.

Fraud

Fraud is another matter. This achieved such publicity in the United States that a Subcommittee of Congress was set up in 1981, with Representative Albert Gore as chairman, to enquire into cheating in scientific work (Broad 1981, *Nature* 1981). The aetiology of scientific fraud is complex, but no doubt one of the most important factors is the need for young men to get their names in print. The Duke of Wellington, threatened with publication of a supposed illicit association with the courtesan, Harriette Wilson, is reputed to have replied to the blackmailing John Joseph Stockdale, 'Publish and be damned'. Nowadays, ambitious young research workers are encouraged to publish or be damned (Altman & Melcher 1983).

Plagiarism

This is obnoxious, but easily detected. The best known example is that of Dr Elias A K Alsabti, a microbiologist working in Dr E Frederick Wheelock's department at Jefferson Medical College in Philadelphia. He was dismissed because an internal audit revealed that he had invented data, and after his dismissal it was discovered that he had published at least seven papers in obscure journals which he had copied almost word for word from other people's publications.

The story of Vijay Soman and his plagiarism is told in full by Broad & Wade (1982). Soman arrived in the United States in 1971 from Poona. After four years at Albany Medical College he won a Fellowship to Yale where, among other things, he proposed studying insulin binding in patients with anorexia nervosa. In November 1978 his chief, Professor Philip Felig, was sent a manuscript to review by the *New England Journal of Medicine*. He asked Soman's opinion and he, unbeknown to Felig, made a copy. The manuscript was entitled 'Insulin receptor abnormalities in anorexia nervosa: mirror image of obesity' and was the work of a Brazilian research worker at the National Institutes of Health, Helena Wachslicht-Rodbard. Felig recommended rejection of the paper, but the Editor of the *New England Journal of Medicine* sought a further opinion and Helena Rodbard's paper was finally accepted and published.

In December 1978 Soman sent a paper entitled 'Insulin binding to monocytes and insulin sensitivity in anorexia nervosa' to the *American Journal of Medicine*. This manuscript was sent by a quirk of chance to Dr Rodbard's chief at NIH who passed it on to her. 'She was aghast. Here was her paper, complete with verbatim passages and even a formula she had devised for working out the number of receptor sites per cell'.

Soman's paper was published in the *American Journal of Medicine* in January 1980. The tale was not, however, finished because – at the insistence of Dr Rodbard and her chief, Dr Roth – first, Dr Jeffrey Flier, and subsequently Dr Jerrold Olefsky, were invited by the Dean of Yale to carry out audits of Soman's work. These revealed that a good deal of the research on insulin binding could not be verified from original data books and a retraction of Soman's paper was issued from Yale. Had it not been for Dr Rodbard's persistence, the full extent of Soman's fraud would never have been uncovered.

Falsification

Falsification is a more serious offence because it can go undetected for a long time, even though it is usually discovered in the end when other workers fail to replicate the findings. In 1960 Melvin Simpson and a postgraduate student published a paper on work done by the student which claimed to show cell-free synthesis of cytochrome C. This could not be substantiated by other workers and Simpson himself published a retraction in 1961.

In the *New England Journal of Medicine* in 1983, two retractions of published papers and an editorial (Relman 1983) appeared. These papers came from Emory University, Atlanta, Georgia, and were the work of John R Darsee, although both of them had co-authors. Dr Darsee subsequently moved to Boston where he worked in the cardiac research laboratory of the Brigham and Women's Hospital. In 1981 suspicion was aroused that he had fabricated data and investigations showed that he had started falsifying as a medical student, had continued to do so during his residency at Emory University, and was only discovered when he moved to Boston. While at Emory his fabrications compromised the integrity of at least eight published papers, all of which are being retracted. At Harvard his cheating invalidated nine published papers. During this time he appears to have manipulated or invented the data in no less than 53 abstracts.

Among the conclusions of the Association of American Colleges Ad Hoc Committee on the Maintenance of High Ethical Standards in the Conduct of Research (Relman 1983) was that:

'The principal deterrent in research fraud is the overwhelming probability that fraudulent data will be detected soon after their presentation.'

This, however, is far too sanguine. Only one letter of disagreement with any of Darsee's fraudulent papers was published, and the authors of that letter did not suggest that the discrepancy could have arisen by fraud. To scientists, such a suggestion is unthinkable. Most editors send submitted papers to referees, and this might be thought to prevent publication of fraudulent material but, as Relman (1983) pointed out:

'Unless a maladroit cheat fabricates results that are manifestly impossible or inherently contradictory, even the most rigorous peer review is not likely to uncover fraud.'

It is, of course, the responsibility of the head of department to make sure that no fraudulent publications come out of his unit. Occasionally, however, one suspects that the name of the head of department is included among the co-authors in papers the raw data of which he has not verified. Readers are, unfortunately, more likely to be taken in by papers with several authors because it is thought that collusion in cheating is unlikely.

Fraud in clinical trials

In controlled clinical trials anomalous results may be concealed by over-zealous interpretations of the protocol, allowing withdrawal of certain patients. The rule must be that the number of, reasons for, and fate of, all withdrawals must be stated.

Actual fraud in clinical trials is probably rare, but its effects can be devastating because it is almost impossible to detect. In 1978 five colleagues of Dr Marc Straus told Boston University that there were inaccuracies in the data on many of the 200 patients which Straus had submitted to the Eastern Cooperative Oncology Group (Broad 1981). The *Boston Globe* got wind of this story and revealed that the falsifications ranged from changing a patient's birth date to reporting laboratory studies and treatments that were never carried out, and even inventing a tumour in a patient who had none.

Multicentre trials can seldom be replicated, owing to the enormous costs involved, and the only way to prevent a repetition of the Straus affair is to conduct random audits and to rely on the detective work of laboratory assistants and scientific rivals. The fact that the possibility of fraud is taken seriously in the United States is indicated by the regulation introduced in November 1980 which allows the National Institutes of Health to cut off the grants of an entire institution if just one researcher is caught misusing grant money or falsifying reports.

Albert Gore's Subcommittee of Congress also found disturbing evidence of deliberate falsification in relation to the testing of new drugs in open or controlled clinical studies. Not only did it find that ineligible patients were sometimes included but, of even greater importance, that some independent contracting laboratories which had been set the task of assessing the safety of new drugs had deliberately suppressed evidence of toxicity (Broad & Wade 1982).

Responsibility of editors and referees

It is the responsibility of journal editors and their referees to be constantly aware of the possibility of bias and fraud and to take all possible steps to prevent publication of papers suspected of these sins. On the other hand, in the words of the anonymous editorial in *Nature* (1981):

'It would be catastrophic if journals habitually declined to give house room to data that could not be accommodated within the existing body of received wisdom.'

There must, however, be occasions when an editor might require, not necessarily for publication, a more detailed account of all exclusions and withdrawals, a detailed table of the patients who suffered a significant event, or even the loan of all the proformas of the patients in a trial. It is, however, a fact that an author's good reputation or attractive theory may discourage such close scrutiny of a paper.

Richard Owen (1982) wrote an amusing, but fundamentally serious, account of reader bias in which he listed 25 reasons why readers (including editors) may be biased to accept (or reject) the conclusions of a research paper. These include rivalry bias, prominent author bias, famous institution bias, flashy title bias, esteemed professor bias, friendship bias and (rarely) benevolence bias.

Conclusions

Bias in clinical trials can be avoided by adhering to certain well-defined rules (Evans & Pollock 1985). There is, however, no hope for the investigator who is prepared to indulge in dishonesty, and the only guarantee that fraudulent data will not be published is to maintain open communications among all members of the team involved in research. Fraud is probably extremely rare, but the merest hint of it is enough to destroy a reputation.

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